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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/016,324	12/10/2001	Francis J. Martin	55325-8148.US06	4133

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EXAMINER
KISHORE, GOLLAMUDI S

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 03/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/016,324	Applicant(s) Martin
	Examiner Gollamudi Kishore	Art Unit 1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 10, 2003* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *29-59* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *29-59* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The request for the extension of time and amendment dated 1-10-03 are acknowledged.

Claims included in the prosecution are 29-59.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> **A person shall be entitled to a patent unless -**
>
> **(e) the invention was described in-**
> **(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or**
> **(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).**

2. Claims 29-31, 33-37, 39 and 40-45 are rejected under 35 U.S.C. 102(e) as being anticipated by Marshall (5,939,401).

Marshall discloses liposome formulations containing a cationic amphiphile, DOPE and PEG (5000)-DMPE for the administration of therapeutic molecules by inhalation. The biological molecules include proteins, small molecules, RNA and DNA. The cationic lipids include cholesterol carbamate derivatives (note the abstract, col. 34, line 27 et seq., col. 54, line 31 et. Seq.).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant points out columns 15 and 33 of Marshall and argue that Marshall's structures are complexes and not liposomes. This argument is not found to be persuasive since Marshall's statements on col. 33, lines 33-49 pointed out by applicant himself, do not exclude the formation of liposomes also in his formulation. Marshall's statement only infer that structures other than highly organized vesicles are also effective. This statement does in no way infers that liposome structures are not present in Marshal and the presence of other structures are not excluded by the claim language in instant claims. Applicant argues that Marshall fails to teach a liposome having a coating of hydrophilic polymer chains on its surface. This argument is not found to be persuasive since Marshall's formulations contain PEG-DMPE; since as pointed out above, Marshall's formulations also include liposomal structures, it is implicit that the hydrophilic polymer structures extend outside the surface of the liposomes and therefore, the outer surface of the liposomes are coated. Instant claims do not require that the coating be continuous over the surface. Applicant's arguments that Marshall's formulations do not have a biologically active agent are not found to be persuasive since Marshall on columns 33 and 34 describe the presence of biologically active agent.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

4. Claims 29-30, 34-37, 39-41, 44-49 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 86/06959 in combination with Klibanov (J. Liposome Research, 1992) both are of record.

WO 86 teaches liposomal formulations and a method of administering the formulations by inhalation. The liposomes are made from a variety of phospholipid combinations and having sizes of less than 5 microns. The encapsulated drugs include interferon (note the abstract, pages 8, 11, 12, 14, 19, 27, 28 and Examples). What is lacking in WO 86 is the teaching of the coating of the liposomal surface with a hydrophilic polymer.

Klibanov teaches that when the liposomal surface is coated with a hydrophilic layer of oligosaccharides, glycoproteins, polysaccharides and synthetic polymers such as PEG, the liposomes avoid the RES and circulate in blood for longer periods. Klibanov further teaches the targeting the liposomes using ligands such as biotin, proteins and antibodies (note the entire publication).

The coat the liposomes of WO 86 with a hydrophilic polymer would have been obvious to one of ordinary skill in the art because such a coating would enable the liposomes to circulate longer and reach the target tissue as taught by Klibanov.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that the purpose of the hydrophilic polymer is to shield the liposomes from RES whereas in Mihalko, the liposomes are administered by inhalation and therefore, there is no motivation to combine. This argument is not found to be persuasive since although the administration in Mihalko is by inhalation (just as in instant application), the purpose is to deliver the drug systemically and the inhaled drug in the liposomal formulation enters the blood for circulation. Therefore, it is reasonable to expect the hydrophilic polymer to protect the liposomes in the blood from entering the RES and removed from circulation. Applicant's arguments with regard to the sizes of liposomes in Mihalko are not found to be persuasive since the statement on page 14, lines 14-15 indicate the less crucial nature of the liposomal sizes.

5. Claims 29-31, 33-37, 39 and 40-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marshall cited above by itself or in combination with WO 86/06959 cited above.

As pointed out above, Marshall discloses liposome formulations containing a cationic amphiphile, DOPE and PEG (5000)-DMPE for the administration of therapeutic molecules by inhalation. The biological molecules include proteins, small molecules, RNA

and DNA. The cationic lipids include cholesterol carbamate derivatives (note the abstract, col. 34, line 27 et seq., col. 54, line 31 et. Seq.). Marshall does not provide a specific example showing the administration by inhalation. It would have been obvious to one of ordinary skill in the art to use this mode of administration of liposomes suggested by Marshall since the mode of administration is the choice of the practitioner. One of ordinary skill in the art would be motivated to use the inhalation route since WO shows the this route as a successful mode of administration of liposomes.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments with regard to Marshall have been addressed above. Applicant once again argues about the sizes of the liposomes in Mihalko. These arguments are not found to be persuasive since as pointed out above, the statement of Mihalko on page 14 indicate the less crucial nature of the liposomal sizes.

6. Claims 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marshall cited above by itself or in combination with WO 86/06959 cited above, further in view of Gao (BBRC, 1991).

Marshall teaches cholesterol derivatives, but not instantly claimed dimethylaminoethane carbamoyl cholesterol.

Gao teaches that instant carbamoyl cholesterol in liposomes is very effective transfecting agent (note the abstract). It would have been obvious to one of ordinary skill

in the art to use instant carbamyl cholesterol derivative in Marshall's liposomes since Gao teaches that this cationic lipid is an effective transfection agent.

Applicant's arguments that the teachings of Gao and Huang do not make up the deficiencies since they make no mention of hydrophilic polymer chains or of coating a liposome with hydrophilic chains are not found to be persuasive since these references have been combined for the teachings of carbamyl cholesterol derivative since this cationic lipid is an effective transfection agent.

7. Claims 49-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 86/06959 in combination with Klibanov (J. Liposome Research, 1992) both are of record, further in view of Chestnut (5,800,815), DeFrees (5,604,207) and applicant's statements of prior art.

The teachings of WO and Klibanov have been discussed above. Neither WO nor Klibanov teach instantly claimed antibodies and ligands.

Chestnut teaches targeting of liposomes using selectin antibodies (note col. 21).

DeFrees teaches targeting of liposomes using sialyl Le (note columns 47 and 48).

Applicants indicate that the claimed antibodies and other ligands are art known (see Table I on page 23).

It would have been obvious to one of ordinary skill in the art to use art known ligands in the teachings of WO and Klibanov since Klibanov teaches that targeting ligands such as proteins and antibodies can be attached to the liposomal surface and the references

of Chestnut and DeFrees further provide guidance as to use of the ligands such as selectin antibodies and sialyl Le along with liposomes.

Applicant's arguments that the teachings of Chestnut, and DeFrees do not make up the deficiencies since they make no mention of hydrophilic polymer chains or of coating a liposome with hydrophilic chains are not found to be persuasive since these references have been combined for the teachings of targeting ligands.

8. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *G.S. Kishore* whose telephone number is (703) 308-2440.

The examiner can normally be reached on Monday-Thursday from 6:30 A.M. to 4:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, T.K. Page, can be reached on (703)308-2927. The fax phone number for this Group is (703)305-3592.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [thurman.page@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-1235.

Gollamudi S. Kishore, Ph. D

Primary Examiner

Group 1600

gsk

March 24, 2003